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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,542	03/02/2007	David Wallach	WALLACH34	3237

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EXAMINER	
STOICA, ELLY GERALD	
ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,542	WALLACH ET AL.	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-58* is/are pending in the application.

4a) Of the above claim(s) *26-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 May 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/27/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I (claims 21-25), and of the species B-CLL, in the reply filed on 10/30/208 is acknowledged. Claims 21-58 are pending. Claims 26-58 are withdrawn as being drawn to non-elected inventions. Claims 21-25 are currently examined.

Drawings

2. The drawings are objected to because there are discrepancies between the legend in the specification and the text in the figure. Specifically, in figure 2c, the specification recites Ramos cells while the figure denotes Raji cells. In figure 3i, the western blot does not support the explanation of the drawing given in the specification. The same applies for figure 4b, since the figure is of such a poor quality that nothing can be seen. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Applicants are reminded to avoid the introduction of new matter in making the corrections. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several

views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

3. Claims 21, 22, 24 and 25 are objected to because of the following informalities: acronyms are used without their full terms at the first incidence. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 21-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a method of treating an immune disorder comprising administering to an individual having the immune disorder a therapeutically effective amount of an agent capable of increasing or decreasing NIK-SIVA complex formation, thereby treating the immune disorder in the individual. The immune disorder is characterized by abnormal function or level of at least one protein selected from the group consisting of BlyS/BAFF, CD27, SIVA and NIK and the elected disorder is B-cells chronic lymphocytic leukemia (B-CLL). Also claimed is a method where the systemic administering is effected by expressing the agent **within** cells of the individual. As such, the method is based on the premise of the existence of a disease that caused by an imbalance in the complex NIK-SIVA formation and the hypothesis that, providing that such disease exists, the modulation of the respective complex would by itself treat the particular disease. Also hypothesized is that expressing the claimed agent in the cells

of a diseased individual (and thus accomplishing gene therapy) would be feasible as a method of treatment.

The prior art is aware of methods of inhibiting either the levels of expression or activity of NIK and SIVA respectively (e.g.: Audrey et al. U.S. Pub. No. 20030092044 – ([0305]); Rothe et al. U.S. Pat. No. 5,843,721-cited by Applicant – abstract and summary of invention; Wallach et al., WIPO/2003/087374, 10-2003, and p. 18-20: Kanteti et al., U.S. Pat. No. 6,010,853, col., 35, lines 14-61, col. 37 lines 11-35). Also, treatment of leukemias by tyrosine kinase inhibitors was known in the art (e.g., Joske DJL, Med. J. Aust., 189,277-282, 2008). However, the prior art does not show interaction between NIK and SIVA and a link between this interaction and any disease.

While the level of skill in the art of in vitro inhibiting interaction between intracellular proteins is high, the relative skill to inhibit such interaction in living organisms is low, especially in the absence of any disease or condition to be treated. That is because the predictability of the in vivo methods for successfully delivering agents that would modulate the interaction between two intracellular proteins is extremely **low.** In this respect, a skilled artisan would have to introduce in a living organism (i.e. not in cell culture) antibodies that might potentially block the interaction by binding to any of the interacting partners or nucleic acids that would block translation of RNA in to the proteins of interest. None of these procedures have been successfully used to treat any disease *in vivo* and serious hurdles would have to be considered (Richardson et al, Gene therapy, 5, 635-644, 1998; Lo et al. Handb. Exp Pharmacol. 181, 343-373, 2008). Also the procedures need to be directed to specific cells since a

generalized administration of the agent to all the cells of the body, given the centrality of the NIK in signaling pathways in normal cells, would potentially represent a harmful situation for the organism. All the procedures would have been performed without the certitude that the interaction between NIK-SIVA is linked to any disease and without the data showing that such a modulation of the interaction would constitute efficient treatment. The guidance provided in the specification is at best at the level of hypothesis to be tested and not as guidance to use a method with likely success. The specification for instance mentions (p. 21, lines 27-30) that upregulation of SIVA-CD27 signaling would overcome myelogenesis. However, this is an untested hypothesis since Katayama et al. (Br J Haematol. 120, 223-234, 2003) states that they were unable to determine if the SIVA protein is pro-apoptotic protein. The language of the specification is highly speculative, providing just a working hypothesis with uncertain outcomes For instance, even of the "working examples", example 6, titled "SPECULATIVE MODEL OF THE MECHANISMS INITIATING NF-κ B ACTIVATION BY TNF AND CD 70" presents no actual working example to verify the model, let alone link it to a method of treatment of a disease. Thus, the teachings set forth in the specification provided no more than a "plan" or "invitation" for those of skill in the art to experiment. It is considered that the amount of experimentation to determine a causative link between Nik-SIVA interaction and a disease and then the treatment of this disease would be enormous, given the hurdles of delivering an agent to the cells intended as recipients (Wendtner et al. Leukemia & Lymphoma, 45, 897-904, 2008).

Also, there are no working models for the treatment of any immune disorder by modulation of the NIK-SIVA interaction, either in the specification or in the prior art.

Due to the large quantity of experimentation necessary to uncover the diseases in which NIK-SIVA interactions are certainly and causatively implicated and then to successfully test therapeutic procedures; the lack of direction/guidance presented in the specification regarding successful methods of treatment; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of treating diseases linked to intracellular protein-protein interaction *in vivo*; and the unpredictability of the link of NIK-SIVA interactions to any disease, undue experimentation would be required of the skilled artisan to use the claimed invention in its full scope.

Conclusion

4. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/

Primary Examiner, Art Unit 1647